ORIGINAL ARTICLE

Pulmonary leptospirosis: an excellent response to bolus methylprednisolone

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Background: This case series analyses the beneficial effect of methylprednisolone in pulmonary leptospirosis, which usually has an aggressive course and grave outcome.
Methods: 30 patients of pulmonary leptospirosis were evaluated. The initial 13 patients did not receive corticosteroids while the remaining 17 all received bolus methylprednisolone one gram intravenously for three days followed by oral prednisolone 1 mg/kg for seven days, on the basis of occasional case reports of benefit in pulmonary leptospirosis. APACHE III and lung injury scores of similar severity were considered while comparing outcomes in those who received methylprednisolone with those who did not.
Results: Dyspnoea and haemoptysis were the commonest symptoms in those with pulmonary manifestations. Overall mortality was 18% (3 of 17) in patients who received methylprednisolone, as compared with 62% (8 of 13 patients) in those who did not ($p<0.02$). In patients with established acute lung injury (ALI score >2.5), five of eight patients survived in the subgroup with corticosteroids (37% mortality) while only one of nine patients survived in the group that did not receive corticosteroids (89% mortality). Corticosteroids affected outcome only if given within the first 12 hours after the onset of pulmonary manifestations. Mortality seemed to correlate with the APACHE scores, and number of quadrants affected on chest radiographs, more than with blood gas pressures.
Conclusions: Corticosteroids reduce mortality and change outcome significantly when used early in the management of pulmonary leptospirosis.

Leptospirosis is a worldwide zoonosis caused by pathogenic species of leptospira—*L interrogans*.[1] Of this serogroup more than 200 serovars have been identified and *L icterohemorrhagica* is associated with the severe form of disease typically presenting as hepatic and renal manifestations known as Weil's disease. Pulmonary manifestations of leptospirosis are frequent,[2] and now being increasingly reported[3 4] with pulmonary haemorrhage as an important cause of death.[5] Although benefits of corticosteroids in acute lung injury and adult respiratory distress syndrome has been extensively studied and accepted,[6 7] evidence for use of corticosteroids in pulmonary leptospirosis is confined to occasional case reports or brief studies.[8–10] In this outbreak of leptospirosis in Mumbai, after unprecedented rainfall and heavy flooding in July 2005,[11] we found an unusual predominance of pulmonary involvement with patients often having dyspnoea as an early symptom and an extremely beneficial role for corticosteroids in these cases.

METHODS

Seventy eight cases of leptospirosis with clinical manifestations were recorded within a short span of the first two weeks of August 2005 after heavy floods in Mumbai. The diagnosis was made by serology using rapid dipstick test for lepto IgM, confirmed by IgM ELISA test.[12] Apart from clinical examination, all patients were subjected to complete blood counts, liver and renal function tests, serum electrolytes, and coagulation screen. All patients also had a chest radiograph PA view, ECG, and an ultrasound of the abdomen.

Thirty patients who had tachypnea, dyspnoea, haemoptysis, or diffuse infiltrates in the chest film were considered to have pulmonary manifestations. They were further evaluated with serial chest radiographs, arterial blood gas measurements, and acute lung injury (ALI) as well as APACHE III scores charted. Compliance, mean and peak airway pressures, positive end expiratory pressure (PEEP), and other respiratory parameters were also recorded in ventilated patients.

All patients received standard treatment with benzyl penicillin at 1.5 MU every six hours and doxycycline 100 mg twice daily. Some patients with fever who had rigors or gave a history of malaria contact in their neighbourhood also received intravenous quinine initially as an empirical measure because of the highly endemic nature of malaria in India. Quinine was given at a dose of 10 mg/kg body weight for up to 48 hours and stopped as soon as serological evidence of leptospirosis and absence of malarial parasites was confirmed.

Invasive pressure monitoring for pulmonary wedge pressures was done in 18 patients, while 11 required ventilator support, and six needed blood component replacement. Six patients were also given dialysis support.

In view of the poor prognosis in the initial 13 patients, and a possible benefit with corticosteroids being known, the next 17 patients were given a trial of bolus methylprednisolone 1 g/day for three days followed by 1 mg/kg/day of oral prednisolone for seven days as a desperate measure to improve outcome.

The outcome in terms of mortality rates was compared in the subset of patients who received methylprednisolone and the subset that did not. Patients with similar severity of disease based on APACHE III scores[13] and ALI scores[14] were compared, to reduce confounding factors like age, underlying chronic diseases, and severity of infection, which could affect the outcome. Statistical significance was proved using the χ^2 test.

In view of the life threatening manifestations and non-availability of an efficacious alternative to methylprednisolone, a randomised control trial, however was not possible.

RESULTS

Pulmonary manifestations were seen in 30 of the 78 patients with leptospirosis (38.46%). Table 1 gives the baseline characteristics of these patients. Age did not correlate with severity or outcome.

Fever was the commonest symptom present in all patients. Dyspnoea was the most common presenting symptom of pulmonary involvement occurring in 23 patients (76.66%). One patient presented with haemoptysis and six others did not have pulmonary manifestations when the chest radiograph showed parenchymal infiltrates. Severe haemoptysis necessitating blood transfusions occurred in only about six patients (20%). Figure 1 gives the incidence of various symptoms in these patients.

Twenty three patients had symptoms or signs attributable to involvement of other systems while seven patients had only pulmonary manifestations. Hepatic involvement with jaundice (S bilrubin >3 mg%) and renal involvement (S creatinine >3.4 mg%) were seen in four patients each, while 15 patients had all three systems affected. Six of these 15 patients also had haematological abnormalities with thrombocytopenia and packed cell volume below 20%. Table 2 shows mortality in those with various organ dysfunction.

APACHE III scores using the worst abnormal value on the first day in the ICU correlated well with outcome, mortality being higher in those with APACHE scores more than 60. The ratio of arterial oxygen to inspired fraction of O_2 (PaO_2/FiO_2) showing severity of acute lung injury did not correlate with either the radiological severity or the pulmonary symptoms. However, the ALI score, which takes both these parameters into account, correlates well with outcome.

Methylprednisolone was given in the remaining 17 patients and their outcome was compared with the earlier 13 patients who had not received the drug. Overall mortality was 11 of 30 patients (36.66%). All 11 patients had ALI score more than 2.5 and eight patients had APACHE III scores above 60.

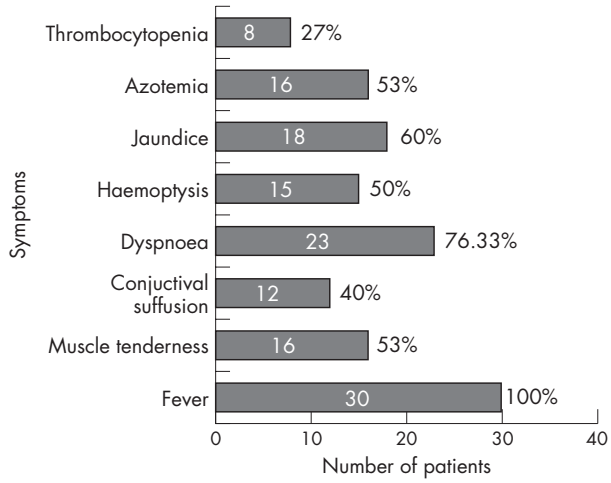

Figure 1 Clinical manifestations of leptospirosis.

In those who received methylprednisolone, mortality was 3 of 17 cases (17.65%), while it was 8 of 13 cases (61.53%) showing a significant benefit for this drug in early course of the disease for pulmonary leptospirosis ($p<0.025$). In severe cases (13 patients) with APACHE III scores more than 60, mortality in the treated group was two of six (33.33%) while in the untreated group it was six of seven cases (85.71%). These figures were significant ($p<0.05$) as shown in figure 2.

In those with ALI score >2.5 that suggested acute respiratory distress syndrome, of a total of 17 patients, eight received methylprednisolone and three died (mortality was 37.5%) while in those who did not receive the drug, mortality

Table 1 Baseline characteristics and summary of all 30 patients

Patient number	Initial	Sex	Age	Primary organ involvement affecting prognosis				Apache III	ALI	Methylprednisolone	Outcome
				Pulmonary	Hepatic	Renal	Haematological				
1	RV	M	16	+		+		32	2.5		S
2	AR	M	26	+		+		45	3		D
3	SJ	M	19	+	+			58	2		S
4	VJ	M	30	+	+	+		73	2.66		D
5	RJ	M	28	+	+	+	+	74	1.5		S
6	SB	M	35	+				46	1.5		S
7	ML	M	23	+	+	+		97	3		D
8	MH	M	28	+				45	1		S
9	ST	F	18	+	+			52	2.75		D
10	MJ	M	35	+	+	+		98	3.66		D
11	BB	M	42	+	+	+		90	2.5		D
12	SD	M	22	+	+	+	+	64	3		D
13	SG	M	21	+	+	+	+	82	2.5		D
14	DP	M	24	+				29	2	P	S
15	MT	M	19	+				41	1.5	P	S
16	GC	M	52	+				44	2	P	S
17	GA	M	22	+		+		49	2.5	P	S
18	SL	M	24	+	+	+		49	1.5	P	S
19	VL	M	28	+		+		52	2.5	P	S
20	DN	M	23	+	+			57	2.33	P	S
21	RA	M	20	+	+			69	2.5	P	S
22	MA	F	40	+				29	2	P	S
23	VP	M	23	+	+	+		46	3	P	S
24	KR	M	60	+	+	+	+	110	2.66	P	D
25	SH	M	18	+	+	+	+	52	2.5	P	D
26	MS	M	25	+				33	2	P	S
27	RZ	M	20	+	+	+		68	2	P	S
28	RM	M	18	+	+	+		65	1.5	P	S
29	VT	M	25	+	+	+		67	2.5	P	S
30	VA	M	30	+	+	+	+	88	2.66	P	D

+, abnormalities of that system.

Table 2 Organ system involvement and mortality

Organ system	Total patients	Deaths	Mortality rate (%)
Only pulmonary (P)	7	0	–
Pulmonary and hepatic (H)	4	1	25
Pulmonary and renal (R)	4	1	25
Pulm + Hep + renal	9	4	44.44
P +H + R and haematological	6	5	83.33

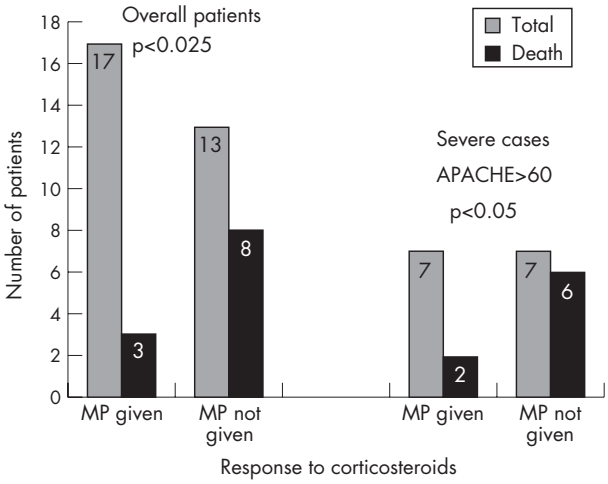

Figure 2 Response to corticosteroids in pulmonary leptospirosis: overall and in severe cases.

was eight of nine patients (88.88%) again significant ($p<0.05$) as shown in figure 3. In those with ALI score $<$ 2.5, all survived irrespective of methylprednisolone.

Mortality correlated very well with the pulmonary quadrant involvement on the chest radiograph. 85.71% of those with four quadrant involvement (six of seven patients) died while mortality was only 26.66% in patients with three quadrant involvement (4 of 15 patients) and 14.28% in two quadrant affliction (one of six patients) and none with single quadrant involvement died. This correlation is significant ($p<0.025$) as shown in figure 4.

Coricosteroids have substantially reduced the need for ventilator support as shown in table 3. Of the seven patients with four quadrant lung injury, four did not receive corticosteroids and died, while of the three who received corticosteroids, one survived without any need for ventilator support. Of 15 patients with three quadrant involvement, 10 patients received corticosteroids and only one needed ventilator support as compared with three of five patients who needed ventilator support without corticosteroids. All four patients who did not receive corticosteroids and had four quadrant involvement died while one of the three patients who received corticosteroids did not need the ventilator and survived.

A total of 11 patients needed ventilator support and only one of these patients with two quadrant involvement survived. A patient with two quadrant involvement on the chest film who was not ventilator supported, died of severe renal involvement and cardiac arrest, probably because of electrolyte imbalance.

DISCUSSION

Ever since the first description of leptospirosis from the Andamans, the disease has been increasingly reported all over India[15 16] and worldwide.[17 18] In most studies the average incidence of pulmonary involvement ranges from 16% to 59.1%.[10] In our case we had an overall incidence of about 38.46%. There was a pronounced male predominance, which is usually found on account of outdoor activity predisposing to disease, more often associated with heavy rainfall or flooding.[19]

Tachypnoea (respiratory rate $>$ 30/min) was the first sign of pulmonary involvement in most patients, although dry cough at some time of hospitalisation was present in nearly 24 patients (80%). Dry cough has been reported to be the commonest symptom of respiratory involvement, especially during the leptospiraemic phase.[20] Haemoptysis occurred in about 15 patients (50%), but was severe enough to cause a decrease in packed cell volume by 2 g% and warrant blood transfusions only in six patients (20%) and platelet transfusions in four patients. Haemorrhagic pneumonitis with frank haemoptysis has been reported in up to 3%–25% of cases,[21] and more recently reported by necropsy to be the commonest

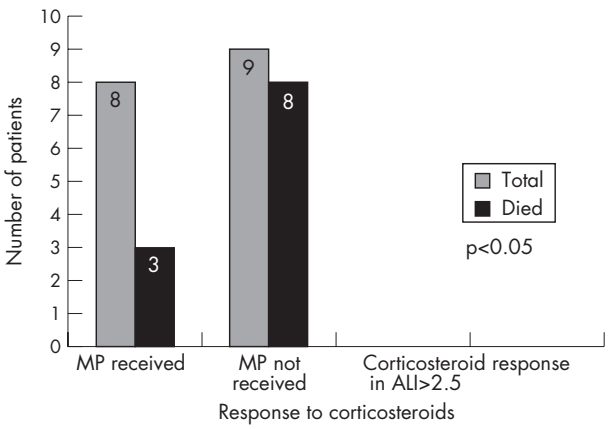

Figure 3 Response to corticosteroids in patients with acute lung injury scores $>$2.5.

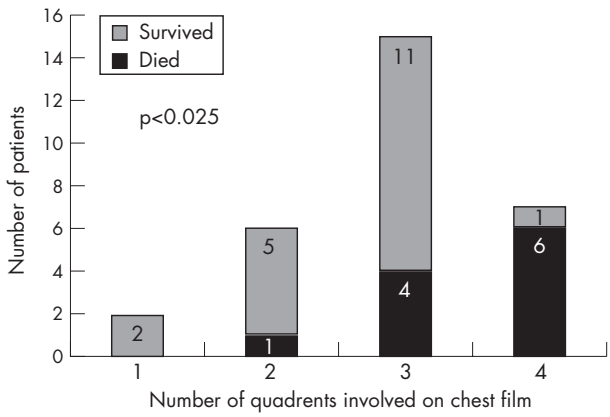

Figure 4 Correlation of mortality with quadrants involved on chest radiograph.

Table 3 Ventilator support requirements in leptospirosis and the effect of corticosteroids

Quadrants on chest radiograph involved	Total patients	Corticosteroids received (ventilator support needed)	Corticosteroids not received (ventilator support needed)
Single	2	1	1
Two	6	3	3 (1)
Three	15	10 (1)	5 (3)
Four	7	3 (2)	4 (4)

Figures in parentheses in both the groups show the number of patients who needed ventilator support.

cause of mortality in patients of leptospirosis.[22] Another study has also suggested highest mortality in those with ARDS and pulmonary haemorrhages.[23]

A study by Marotto *et al* from Brazil has elucidated haemodynamic disturbances and serum creatinine and potassium concentrations to correlate with mortality.[24] We did not find any correlation between biochemical factors and outcome. Although mortality in those with pulmonary affliction was higher (11 of 30 or 36.66%) than overall mortality (16 of 78 or 20.51%) closer analysis shows that those with only pulmonary manifestations had ALI scores less than 2.5, suggesting mild disease and none succumbed, while those with concomitant renal as well as hepatic derangement had aggressive pulmonary involvement and suffered a mortality of almost 44%. This may also be attributable to the fact that five of these seven patients with isolated pulmonary involvement were in the latter part of the series, thereby suspected earlier and also given corticosteroids. The worst outcome however was in patients with pulmonary, hepatic, renal, and haematological disturbances, with multiple organ failure wherein five of the six patients died. Mortality was 83% despite three patients having received corticosteroids, although late in the course of disease.

It is well known that all the systemic manifestations of leptospirosis like hepatic dysfunction, aseptic meningitis, myocarditis, which occur in the second week of infection, are immunologically mediated.[1]. Although the pathogenesis of pulmonary manifestations is poorly understood, infectious vasculitis is believed to be responsible.[2 19] This pulmonary vascular injury is probably attributable to a disseminated intravascular coagulation-like reaction to leptospira toxins mediated by tumour necrosis factor.[25] Values of soluble interleukin 2 receptor concentrations are high and correlate with the clinical course of leptospirosis.[26]

Therefore, although the role of corticosteroids has always been considered, no randomised trials have been possible on account of the life threatening nature of the disease and non-availability of alternative confirmed treatment. Courtin *et al* from France probably first described a good response to bolus corticosteroids in pulmonary leptospirosis.[8] Trivedi *et al* have reported the favourable outcome to pulse glucocorticoid therapy using dexamethasone for three days followed by oral prednisolone 1 mg/kg/day for seven days.[10] However, only eight patients received the drug and statistical calculations remain unknown. Udwadia has again emphasised the beneficial role of pulse glucorticoids in severe pulmonary leptospirosis as seen anecdotally in practice.[9]

Key points

- Bolus methyl prednisolone given within the first 12 hours of onset of respiratory involvement is life saving in pulmonary leptospirosis, more so in severe disease. It also reduces or delays the need for ventilator support and serves an important role in infrastructure limited settings.
- The number of quadrants involved on chest radiograph attributable to acute lung injury correlates with the outcome in leptospirosis, four quadrant involvement being an indicator of poor prognosis.

In our study the initial 13 patients did not receive corticosteroids and had an alarming mortality of over 60% and hence we decided to use corticosteroids in the following 17 patients on the basis of the above literature. The results were outstanding with a reduction in mortality to about 17.65%, which was statistically significant. These results were equally significant in those with severe disease with APACHE scores >60 with mortality being 85.71% in the seven patients who did not receive corticosteroids as compared with 33.33% in the group of six patients that received methylprednisolone.

ALI score >2.5 has been known to correlate with severe respiratory distress and a higher mortality.[14] Of 17 patients with ALI score >2.5, eight patients received corticosteroids with a 37.5% mortality while in those who did not receive corticosteroids mortality was 88.88% suggesting a strong role for methylprednisolone in those with severe lung injury. All patients with mild lung involvement with ALI score <2.5 survived irrespective of methylprednisolone.

All the three patients who died despite receiving corticosteroids presented to hospital more than 12 hours after onset of dyspnoea suggesting that the delay in presentation to hospital and time to administration of corticosteroids after onset of dyspnoea is an important factor affecting outcome. Trivedi *et al* recorded a similar finding with higher mortality in patients who received corticosteroids more than 10 hours after onset of dyspnoea.[10]

The severity of pulmonary involvement can be assessed by abnormalities on a chest radiograph. To permit a quantitative estimate of severity and permit comparisons, the standard chest film is usually divided into four quadrants. The number of quadrants involved are also a component of the ALI score.[14] We found a strong statistically significant correlation of mortality with the number of quadrants involved on the first chest radiograph at presentation. However, this assessment of number of quadrants involved should be necessarily done by a radiologist to reduce subjective variations and minimise discrepancies.[27] Although such a correlation has not been previously described, this needs further evaluation as it is an easily available and cost effective indicator of outcome. Hypoxia or arterial blood gas pressures (PaO_2/FiO_2 ratio) do not correlate with radiological severity and do not predict outcome.[28] Corticosteroids also reduced the need for ventilator support as shown in table 3 where only 3 of 17 patients who received bolus corticosteroids needed mechanical ventilation as compared with 8 of 13 patients without corticosteroids. However, mortality of patients already receiving ventilator support did not change with corticosteroids again emphasising their role only in the early course of disease. All mortality on ventilator related patients were within 48 hours of initiating mechanical ventilation and therefore the chance of ventilator associated infections adding to mortality was unlikely. Requirement for ventilator

support is another indicator for poor outcome in pulmonary leptospirosis.

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